COMMENTS ON THE EPA DRAFT AND FINAL RISK ASSESSMENTS ON ETS

In June, 1990, the United States Environmental Protection Agency (EPA) released for review a Draft Risk Assessment on ETS.[1] The 1990 Draft Risk Assessment concluded that exposure to ETS is causally related to lung cancer in adult nonsmokers and is associated with respiratory disease and respiratory symptoms in children. The 1990 Draft Risk Assessment also concluded that ETS should be classified as a Group A ("known human") carcinogen. It estimated that ETS exposures are responsible for 3,800 nonsmoker lung cancer deaths per year in the U.S. (The estimate was later revised to 3,700). The Science Advisory Board (SAB) for the EPA reviewed the 1990 Risk Assessment in a meeting in December, 1990. Their report, presented to the SAB Executive Committee in April, 1991, suggested that while further revisions were needed, the conclusions of the Draft were sound.

In May, 1992, the EPA released a revised Draft Risk Assessment on ETS.[2] The revised Draft Risk Assessment again concluded that exposure to ETS is causally related to lung cancer in adult nonsmokers. The revised Draft also concluded that ETS exposures are causally related to respiratory diseases and symptoms in children and added numerical estimates of risk for various respiratory conditions. The revised Draft Risk Assessment again concluded that ETS should be classified as a Group A ("known human") carcinogen. The revised Draft was reviewed by the EPA's SAB

Committee in July, 1992. More charges for revisions were made to the EPA staff, but the committee once again endorsed the Draft's conclusion. An Executive Committee meeting of the EPA-SAB took place in October, 1992. The Executive Committee endorsed the SAB committee's report, and the Draft was sent back to EPA staff for minor revisions.

On Thursday, January 7, 1993, at a press conference, EPA Administrator William Reilly and Secretary Sullivan of the Department of Health and Human Services released the final EPA document, entitled, "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders."[3] The document classifies ETS a Group A ("known human") carcinogen.

All three versions of the EPA Risk Assessment employ a Population-Attributable Risk model for estimating excess lung cancer mortality among nonsmokers reportedly exposed to ETS.[1,2,3] This model is based essentially upon three estimates:

1. a point estimate or relative risk derived from a meta-analysis of epidemiologic studies on nonsmoking wives married to smokers;
2. the proportion of nonsmokers in the general (U.S.) population reportedly exposed to ETS; and
3. the total number of nonsmokers in the general population.

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To calculate the Population-Attributable Risk (PAR), the authors of the 1990 Draft Risk Assessment estimated that 60% of all nonsmokers are exposed to ETS. A cumulative relative risk of 1.28 was calculated in the 1990 Draft via meta-analysis from epidemiologic studies on spousal smoking as the estimated excess risk due to ETS exposure. The PAR for these two assumptions (with other minor adjustments) is 0.27. The total number of deaths for nonsmoking males and females was then estimated, based on the American Cancer Society's projections for 1988 (9,500 total deaths). By multiplying the PAR (0.27) by 9,500, the authors generated an estimate of 2,560 total deaths per year attributable to ETS exposure among neversmokers. A PAR was also computed for male and female former smokers, generating a total estimate of 3,800 excess deaths annually purportedly attributable to ETS exposure among nonsmokers in the United States. Using the same procedure in the 1992 Draft, the authors performed a meta-analysis of the then available eleven U.S. spousal smoking studies, combined the studies results and estimated a relative risk of 1.19. The calculated cumulative risk generates an estimate of 3,000 excess deaths per year among nonsmokers. The EPA did not modify its 1992 Draft estimate in the final risk assessment document.

The PAR method employs estimates of relative risk, population fractions of exposure to ETS and lung cancer death rates for the general nonsmoking population in order to generate an

estimate of excess mortality reportedly attributable to ETS exposure. It is important to note at the outset that the PAR model itself does not determine that there is an increased risk of lung cancer among nonsmokers from ETS exposure. Rather, the model assumes a causal relationship between ETS exposure and an increased risk of lung cancer among nonsmokers, based upon increased risks reported in epidemiologic studies on spousal smoking. These reported relative risks are, in turn, assumed to represent true relative risks for the entire population due to ETS exposure.

These critical assumptions have been challenged.[4] To achieve a cumulative excess risk estimate of 1.28 for nonsmokers reportedly exposed to ETS, the authors of the 1990 Draft Risk Assessment performed a meta-analysis of 23 epidemiologic studies on spousal smoking. Eighteen of the studies on spousal smoking included in the EPA's 1990 meta-analysis report overall risk estimates that fail to achieve statistical significance and are, therefore, consistent with the null hypothesis of no association between spousal smoking and lung cancer among nonsmokers.

The meta-analysis in the 1992 Draft was performed on eleven U.S. spousal smoking studies, none of which originally reported an overall statistically significant risk estimate. Nevertheless, the EPA combined the results of the studies, which generated a summary risk estimate of 1.19 for nonsmoker lung cancer.

The EPA reported that its risk estimate was statistically significant, obtained by reanalyzing the data from the original studies and applying a lower standard for statistical significance (a 90% confidence interval). The EPA justified their choice of the 90% confidence interval as consistent with a "one-tailed" statistical test. The one-tailed test, however, presumes causation: it is designed to show the extent of a purported "effect."

The choice of confidence interval was criticized in a presentation at the October SAB Executive Committee meeting, by James J. Tozzi. In a follow-up letter to the EPA, Tozzi included a meta-analysis of 13 available U.S. studies which is not statistically significant using the standard 95% confidence interval.[5] Tozzi reported a relative risk estimate of 1.07 (95% C.I.: 0.95 to 1.21). The EPA did not choose to modify their statistical calculations in the final risk assessment document. The meta-analysis submitted by Tozzi included two additional lung cancer studies that did not report an overall statistically significant association between spousal smoking and lung cancer. The EPA omitted from its risk assessment the NCI-funded Brownson et al., 1992, study, one of the largest and most recent studies on ETS and lung cancer, which reported no increase in risk for spousal smoking.[6] They also omitted the Stockwell et al., 1992, study.[7] If the EPA had considered the Brownson and Stockwell data, its

meta-analysis would not have resulted in a statistically significant increased risk estimate for spousal smoking.

Eleven of the epidemiological studies EPA considered in the 1992 Draft Risk Assessment also included estimates of workplace exposures, but the EPA did not assess the data from those studies. Ten of those eleven studies reported no statistically significant increased risk for nonsmoking females. If the data on workplace exposures are pooled in a meta-analysis, the risk estimate approximates 1.00 (unity), which indicates no positive association between reported workplace exposures to ETS and lung cancer in nonsmokers.

The epidemiologic studies on spousal smoking contain no actual exposure data on ETS. The 1990 and 1992 EPA Drafts assumed the validity of questionnaire responses about possible exposure to ETS based upon spousal smoking and then generalized those responses to estimate the general population's exposure to ETS. The authors of the 1990 and 1992 Draft Risk Assessments also failed to adequately consider and adjust for confounding factors, e.g., diet, lifestyle, genetics, etc., in the individual studies on spousal smoking. This is a significant oversight, especially when dealing with "weak" relative risks which approximate 1.3 in the 1990 Draft Risk Assessment and only 1.19 in the 1992 Draft. When dealing with relative risks this small, spurious associations may be

reported between two factors. For example, because the EPA did not adequately address the potential role of diet, there is a chance that the association the EPA reported between ETS exposure and nonsmoker lung cancer may actually be a result of a common association the two factors may have with poor diet.

The Draft's assumption of causality is based upon tenuous data from epidemiologic studies on spousal smoking. The assumption is the critical element to the PAR model and the original estimate of 3,800 (and revised estimate of 3,000) excess nonsmoker deaths per year reportedly due to ETS exposure. The 1990 and 1992 Draft Risk Assessments fail to argue convincingly for the assumption. Without the causal assumption, the PAR approach is little more than an exercise in mathematical modeling.

The conclusions of the 1990 Draft Risk Assessment were strongly criticized, particularly in many of the more than 100 comments submitted during the public comment period on the draft.[4] Specifically, many of the public comments found EPA's classification of ETS as a Group A carcinogen to be scientifically unwarranted.

One point of criticism was that the EPA's proposed classification of tobacco smoke as a "human carcinogen" was based in part upon the imputed identification and presence in ETS of suspected carcinogens reported in mainstream smoke and/or fresh

sidestream smoke. However, the EPA apparently did not review the available published data on either the characterization of, or exposure to, ETS in its hazard identification. ETS is neither chemically nor physically equivalent to either mainstream or sidestream smoke, and it is therefore not scientifically acceptable to treat ETS, mainstream smoke and sidestream smoke as physically and quantitatively similar mixtures.[8-13]

As discussed above, meta-analysis, a statistical procedure which combines the reported risk estimates from a number of studies to generate an overall estimate of risk, was used in the EPA's Population-Attributable Risk model. The problems and limitations of the use of meta-analysis for epidemiologic studies have been addressed in the scientific literature.[14,15] For instance, meta-analysis does not account for intrinsic bias and confounding in the individual studies, and it cannot remedy study design flaws. As two German scientists, Heinz Letzel and Karl Uberla, noted: "Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers."[15] The spousal smoking studies used in the 1990 meta-analysis were conducted in the United States, Europe and Asia. These populations differ genetically and in lifestyle factors, and the studies themselves differ in design.[14] The 1992 Draft included separate meta-analyses for the different countries and regions.

Another major criticism of the 1990 Draft Risk Assessment was that in addition to its inadequate treatment of the data on the physical and chemical properties of ETS, it also virtually ignored the available exposure data, toxicological data and data from animal studies on ETS. The 1992 Draft similarly failed to consider these data. For instance, not one of the spousal smoking studies included actual measurements of ETS exposure; exposure was only estimated by responses to questionnaires. However, a large body of literature exists on actual measurements of ETS in indoor environments, which was not considered in the 1990 Draft Risk Assessment and only cursorily considered in the 1992 Draft.[5,15-19] While these data are independent of the epidemiologic literature, they suggest that nonsmoker exposure to ETS in typical public places and workplaces is minimal.[17-21] For example, some studies report typical measurements of nicotine ranging from an exposure equivalent of 1/100 to less than 1/1,000 of one filter cigarette per hour.[22-29]

While a docket for written comments was not established for the 1992 Risk Assessment, oral comments were allowed at both the July SAB committee and the October Executive Committee meetings. However, commenters were asked not to reiterate previous points of discussion. One major issue raised by Dr. William J. Butler in July was the EPA's treatment of confounders.[30] The EPA took the position that confounders could not account for the reported

association between spousal smoking and nonsmoker lung cancer, since the EPA was unable to find a single confounding factor that could consistently account for the results reported in all of the studies used in the Draft Risk Assessment. Butler criticized the EPA's position and stated that there were many potential confounders that should be considered important, and that it was not necessary (or even reasonable to expect) to identify a single confounder that would apply to all of the individual studies.

Finally, if the EPA had followed its own 1986 guidelines for carcinogen risk assessment, it would have included: (1) a hazard evaluation which would have examined data regarding the physical and chemical characterization of ETS, as well as the results from published animal inhalation studies and human short term tests; (2) an exposure evaluation which would have included and integrated the data from well over 35 studies in the published literature that monitored ETS constituents in the air of public places and workplaces; (3) a dose-response evaluation which would have relied upon the actual data reported in the epidemiologic studies on spousal smoking (and not upon trend tests); and (4) a risk characterization which would have included the range of uncertainty in assumptions and numbers of lung cancer deaths reportedly attributable to ETS exposures. The guidelines also require that chance be ruled out statistically in all epidemiologic

studies under consideration and that all possible biases and possible confounding factors are to be considered.

Thus, the conclusions of the EPA's 1990 and 1992 Draft Risk Assessments are based on an incomplete and selective review of the existing data on ETS. Several of the public comments on the 1990 Draft suggested that this amounted to EPA's apparent failure to follow its own guidelines for carcinogen risk assessment.[4] The EPA could not have classified ETS as a Group A carcinogen had it used the methodologies and guidelines it employed in its previous risk assessments.

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